UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,240	09/19/2003	Tommy Ekstrom	06275-188002	6971

26164 7590 10/18/2007

FISH & RICHARDSON P.C.
P.O BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
CARTER, KENDRA D	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
10/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,240	EKSTROM, TOMMY	
	Examiner	Art Unit	
	Kendra D. Carter	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-29,34,36 and 42-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-29,34,36 and 42-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/367,950.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner acknowledges the Applicant's remarks and arguments of July 27, 2007 made to the office action filed January 30, 2007. Claims 13-29, 34, 36 and 42-51 are pending. Claims 13, 16, 20, 21, 24, 26-29, 34, 36, 42 are amended and claims 43-51 are new.

In light of the amendments to the claims, the 35 U.S.C. 112, first paragraph rejection of claims 13-42 is withdrawn.

The Examiner acknowledges Applicant's indication that a terminal disclaimer will be filed upon identification of allowable subject matter to obviate the provisional obviousness-type double patenting rejections over U.S. Patent Application No. 09/367,950. However, as such terminal disclaimers have not as-yet been filed, the provisional obviousness-type double patenting rejections over these co-pending applications are being maintained.

The Examiner acknowledges the 131 Affidavits filed July 27, 2007 as Exhibits 1-5, but does not find them persuasive to overcome the 35 U.S.C. 103(a) rejections of record.

For the reasons in the previous office action and below, the Applicant's arguments of the 35 U.S.C. 103(a) rejection of claims 13-15, 17, 18, and 20-42 as being

unpatentable over Carling (WO 9311773 A1) were found not persuasive, thus the rejection is upheld.

For the reasons in the previous office action and below, the Applicant's arguments of the 35 U.S.C. 103(a) rejection of claims 16 and 19 as being unpatentable over Carling (WO 9311773 A1) as applied to claims 13-15, 17, 18, and 20-42 above in view of Aberg et al. (U.S.Patent 5,795,564) and in further view of Ryrfeldt et al. (Biochemical Pharmocology, 1989, 38(1), pages 17-22), were found not persuasive, thus the rejection is upheld.

Due to the amendment to the claims, the previously made double patenting rejection and modified 35 U.S.C. 103(a) rejections are made below.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

(1) Claims 13-15, 17, 19, 20, 22-25, 30-36, 38, and 42 are provisionally rejected on the ground of nonstatutory double patenting over claims 13-15, 17, 19, 20, 22-25, 30-36, 38, and 42 of copending Application No. 09/367,950. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

The US Application No. 09/367,950 discloses a method of prevention and treatment of asthma symptoms, which comprises instructing a patient in need thereof to

inhale an effective amount of a composition comprising, in admixture: (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and (b) a second active ingredient which is budesonide; characterized in that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and a preventive measure, when the patient experiences an increase in asthma symptoms (see claim 13). The molar ratio of (a) to (b), calculated as formoterol to budesonide~ is from 1:1 to 1:100 or 1;1 to 1:70 (see claims 14 and 25). The first active ingredient can be formoterol fumarate dihydrate (see claim 15) or the R,R enantiomer of formoteml, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt (see claim 16). Formoterol is in a unit dose of from 1 μg to 48 μg or 1 μg to 100 μg for daily dose, including maintenance therapy, which is calculated as formoterol fumarate dihydrate (see claim 17 and 18). The second active ingredient can be the 22R epimer of budesonide (see claim 19). The budesonide is in the form of a unit dose, which delivers 20 μg to 1600 μg to the patient (see claim 10). The particle size of the active ingredients (a) and (b) is less than 10 μm (see claim 22). The composition additionally comprises one or more pharmaceutically acceptable additives, diluents or carriers (see claim 23). The composition can comprise lactose monohydrate (see claim 24). The patient can be instructed to inhale the composition as a rescue medication, as a complement to maintenance treatment of the patient's asthma, as a preventive measure prior to encountering an asthma triggering event, such as cold air, exercise, and exposure to a smoky environment (see claims 30 and 32-36).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(1) Claims 13-15, 17, 18, and 20-29, 34, 36 and 42-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling (WO 9311773 A1).

Carling et al. teaches suitable daily asthmatic dose of formoterol (as fumarate dehydrate; see page 8, line 6; addresses applicant's claims 13, 15, 17-18, 26-27, 36, 42 and 49-51) and/or a physiologically acceptable salt and/or solvent thereof and budesonide twice a day (i.e. on demand; see page 4, lines 24-28; page 6, lines 5-30, addresses applicant's claims 13, 35, 36, 42 and 49-51). The combination of the two drugs have greater efficiency and duration of bronchodilator action, and rapid onset action, which provides rescue medicine, adequate dosing for treating asthma (see page 4, lines 4-21; addresses applicant's claims 13, 36, 42 and 49-51). This new feature is of

utmost importance in order to establish a higher compliance for patients and it provides a rescue medicine thereby avoiding the necessity for the patient of carrying two different inhalers (see page 4, lines 4-10; addresses claim 48). Formoterol is administered in a suitable daily dose in a range of 6 to 100 μg with a daily dose of budesonide in a range of 50 to 4800 μg (see page 6, lines 24 and 26; addresses applicant's claims 17, 18, 20, 21, and 27-29). The dosages strongly depends on the patient (age, weight etc.), severity of disease (mild, moderate, severe asthma etc..); see page 6, lines 27-29. The ratio of formoterol to budesonide is in the range of 1:4 to 1:70, which can be administered separately in the same ratio (see page 6, lines 17-20; addresses applicant's claims 14, 17, 20, 25, 26, and 28). Non-toxic and chemically inert diluents, additives, and carriers are used in the composition, such as lactose (see page 7, lines 1-3; addresses applicant's claim 23 and 24). The amounts of active agents per dose of inhalation are disclosed on pages 7-9, which calculate up to 8 inhalation per day without going over the maximum daily dosage. For administration, the combination is suitably inhaled from a nebulizer, from a pressurized metered dose inhaler or as a dry powder from a dry powder inhaler (see page 6, last paragraph, addresses claims 43 and 44). The micronized mixture may be suspended in a liquid propellant mixture. The propellants may be chlorofluorocarbons of different chemical formulae. The most frequently used chlorofluorocarbon propellants include tetrafluoroethane (P134a) and 1,1-difluoroethane (P152a; see page 7, lines 15-25; addresses claims 45-47).

Carling et al. does not specifically teach one or more additional doses on an irregular, as-needed basis for rescue purposes, as determined by the patient (claim 13), based on the patient's symptoms, when (1) the patient experiences an increase in asthma symptoms as set forth in applicant's claim 13; or (2) when the patient is expecting to encounter an asthma inducing condition, wherein the inducing condition is selected from the group consisting of exposure to cold air, exposure to pollen, exposure to perfume, exercise, or exposure to a smoky environment (applicant's claims 34, 36, 50 and 51). Carling et al. does not teach to inhale additional doses as needed to improve control and provide acute relief (applicant's claim 42). Carling et. al. also does not teach the particle size of the active ingredients (applicant's claim 22), or the specific propellant P227 (claim 47).

To one of ordinary skill in the art, it would have been obvious to combine the method of Carling et al. and administering the method on an irregular, as-needed basis for rescue purposes, as determined by the patient in any of the circumstances detailed in claims 13, 34, 36, 42 and 49-51 because Carling et al. teaches that the dosages strongly depends on the severity of disease, whether mild, moderate, or sever asthma (see pg 6, lines 27-29), and the suitable daily dosage is up to 8 inhalation (see page 7-9).

The motivation to combine the methods and compositions of Carling et al. and instructing the patient to inhale, on demand in any of the circumstances detailed in claims 13, 34, 36, 42 and 49-51 because Carling et al. teaches that the dosages strongly depends on the severity of disease and to achieve maximum benefit of daily dosage recommended. It is noted by Carling et al. that the combination of formoterol with budesonide is well known to be beneficial for the treatment of asthma (see page 4, lines 4-21). Moreover, if the patient is experiencing acute asthmatic attack even with ongoing twice a day dosing regimen, the patient can still safely inhale an additional 6 inhalations without going over the maximum suitable daily dosage. In general, Carling et al. teaches therapeutic relief from asthmatic attack. The skilled artisan would have been motivated to instruct the patient to use the Carling et al. composition as needed on the bases of up to 8 inhalations a day is for reasonable expectation of successfully achieving maximum benefit in the treatment of any level of the asthma condition, including an increase in asthma symptoms, acute asthmatic condition, maintenance treatment, and common asthma triggers. Additionally, due to the urgency of therapy during an asthma attack, a patient would obviously seek relief with the medication without consulting with the physician, in knowing the safe daily dosage range of each medication.

To one of ordinary skill in the art at the time of the invention would have found it obvious to combine the method of Carling et al. and the particle size of active agents set

forth in claim 22, because they are known by a skilled pharmacologist and represent conventional formulations.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Carling et al. and the specific propellant P227 because Carling et al. teach that the propellants may be chlorofluorocarbons of different chemical formulae. Carling et al. also teaches some of the most frequently used, such as Applicant's claimed tetrafluoroethane (P134a) and 1,1-difluoroethane (P152a; see page 7, lines 15-25; addresses claims 45-47).

(2) Claim 16 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling et al. of record as applied to claims 13-15, 17, 18, and 20-42 above, in view of Aberg et al. (U.S. Patent 5,795,564) and in further view of Ryrfeldt et al. (Biochemical Pharmocology, 1989, 38(1), pages 17-22).

Carling et al. teaching are as applied to claims 13-15, 17, 18, and 20-42 above.

Carling et al. does teach the (R,R) enantiomer of formoterol set forth in claim 16 and the 22R epimer of budesonide set forth in claim 19.

Aberg et al. teaches (R, R) isomer of formoterol as required by claim 16 is a potent bronchodilator with reduced adverse effects in treatment of asthma. (abstract, column, 1, lines 25-35).

Ryrfeldt et al. teaches that the 22R epimer of budesonide is more potent in the treatment of bronchial asthma than 22S epimer (see page 17, column 1, paragraph 2, lines 12-15).

To one of ordinary skill in the art at the time of the invention would have found it obvious to combine the method of Carling et al. and the (R,R) enantiomer of formoterol and the 22R epimer of budesonide because Aberg et al. and Ryrfeldt et al. teach that these specific isomers possess potent asthmatic effect.

The motivation employ the (R,R) isomer of formoterol and 22R epimer of budesonide in the Carling et al. composition is because there is a reasonable expectation of successfully treating asthmatic patients with a more effective medication with reduced adverse effects.

Response to Arguments

35 U.S.C. 103(a) rejections and 131 Affidavits

Applicant's arguments filed July 27, 2007 have been fully considered but they are not persuasive.

The Examiner acknowledges the 131 Affidavits filed July 27, 2007 as Exhibits 1-5, but does not find them persuasive to overcome the 35 U.S.C. 103(a) rejections of record.

> Exhibit 1 is the 1997 copy of the product insert packaged with Plumicort Turbuhaler product, which includes patient's instruction for use of the asthma inhaler. Pulmicort Turbuhaler comprises budesonide as the sole active ingredient. The Applicant points out particular notice to the recommended starting doses and highest recommended doses for various categories of patients are only given dosages to be administered twice daily. Additionally, the Applicant points out the following dosage information: (1) use the product as directed by a doctor; 2) it is very important that you follow your doctor's instructions as to how many inhalations to take and how to use your Pulicort Turbuhaler; 3) do not inhale more doses or use your Pulmicort Turbuhaler more often than your doctor advises; 4) it may take 1 to 2 weeks or longer before you feel maximum improvement so it is very important that you use Pulmicort turbuhaler regularly; and 5) do not stop treatment or reduce your dose even if you are feeling better, unless told to do so by your doctor. The Applicant argues that the above illustrates that the physician, and not the patient determines when the dosage of budesonide can be altered for a given patient. If the patient suffers an exacerbation of symptoms, he must turn to a different type of medication (a short-acting bronchodilator) for immediate relief.

The Examiner disagrees because it is noted that evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention. See, e.g., In re Kulling, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 777 (Fed. Cir. 1983). The present claims are drawn to an admixture of budesonide and formoterol, in which Exhibit 1 only discusses budesonide. Additionally, Carling et al. specifically teach that the combination of budesonide and formoterol have greater efficiency and duration of bronchodilator action, and rapid onset action, which provides rescue medicine, adequate dosing for treating asthma (see page 4, lines 4-21). This new feature is of utmost importance in order to establish a higher compliance for patients and it provides a rescue medicine thereby avoiding the necessity for the patient of carrying two different inhalers (see page 4, lines 4-10). Thus, Exhibit 1 is not persuasive to overcome any of the rejections of record.

> Exhibit 2 is the 2001 product insert of SYMBICORT TURBUHALER, a budesonide/formoterol inhalation powder product. The Applicant points out that the recommended dosage is 1-2 inhalations twice daily, in which when control of symptoms is achieved with the twice daily regimen, the physician can chose to reduce the number of inhalations to one daily (see sections A and B). Further, the insert instructs the dosage should be adjusted to the severity of the disease. If an individual patient should require dosages outside the recommended regimen, appropriate doses of beta-agonist and/or corticosteroids should be prescribed (see section C). The Applicant points out that there is no suggestion anywhere in the document that the patient can choose to self-administer additional doses, beyond the twice daily regiment. To the contrary, use outside of the fixed dosage regimen is dangerous and forbidden: "If patients find the treatment ineffective, or exceed the current dose of the fixed combination, medical attention must be sought." Page 2, section D. Also, "patients should be regularly reassessed by a doctor, so that the dosage of Symbicort

> Turbuhaler remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained." Page 2, section E and page 1, section F, respectively. These instructions clearly indicate that if the patient experiences an increase or decrease in symptoms, the patient is to notify the physician so that the treatment protocol can be reassessed by the physician. Adjusting the dosage from day to day at the patient's discretion is nowhere contemplated.

The Examiner disagrees because as the product insert teaches, the dosage should be adjusted to the severity of the disease. Additionally, if an individual patient *should require dosages outside the recommended regimen, appropriate doses of beta-agonist and/or corticosteroids should be prescribed* (see section C). Furthermore, Carling et al. teach the following: 1) formoterol is administered in a suitable daily dose in a range of 6 to 100 μg with a daily dose of budesonide in a range of 50 to 4800 μg (see page 6, lines 24 and 26); 2) the dosages strongly depends on the patient (age, weight etc.), severity of disease (mild, moderate, severe asthma etc..); see page 6, lines 27-29; 3) the ratio of formoterol to budesonide is in the range of 1:4 to 1:70, which can be administered separately in the same ratio (see page 6, lines 17-20; addresses applicant's claims 14, 17, 20, 25, 26, and 28); and 4) the amounts of active agents per dose of inhalation are disclosed on pages 7-9, which calculate up to 8 inhalation per day without going over the maximum daily dosage. Thus, if the patient is experiencing acute asthmatic attack even with ongoing twice a day dosing regimen, the patient can still safely inhale an additional 6 inhalations without going over the maximum suitable daily dosage. The skilled artisan would have been motivated to instruct the patient to use the Carling et al. composition as needed on the bases of up to 8 inhalations a day is

for reasonable expectation of successfully achieving maximum benefit in the treatment of asthma. Therefore, upon given directions from one skilled in the art (i.e. physician) that the patient can take a certain number of additional doses, based on the patients age, weight and asthma severity, the patient can then self-administer the additional doses as-needed. The as-needed dosages that the doctor approves is with the knowledge of what the maximum daily dose is of each drug and therefore, is safe for each individual patient. In regards to the lowest effective dose being administered, this is common practice among those skilled in the art. Additionally, administering the lowest effective dosage supports that if an individual patient needs more of the drug, the as-needed dosages as discussed above would be given safely since the patient is not at his or her maximum dosage. Thus, Exhibit 2 is not persuasive to overcome any of the rejections of record.

Exhibit 3 is the 2003 patient's instructions for use of ADVAIR DISKUS, which is a fluticasone propionate/salmeterol xinafoate inhalation powder product. The Applicant points out that the insert teaches no to use ADVAIR DISKUS more frequently than 2 times daily, morning and evening, approximately 12 hours apart, at the recommended dose of 1 inhalation each time. Also, the insert teaches to not use ADVAIR DISKUS to relieve sudden asthma symptoms. An inhaled, short-acting broncholidilator such as albuterol should be used to relieve sudden asthma symptoms (see page 2, numbers 2 and 6). The Applicant argues that there is no suggestion anywhere in the document that the patient can choose to self-administer additional doses, and the insert repeatedly teaches that the product must be used neither more nor less often than instructed by the physician (see page 2 of insert). The Applicant further argues that like budesonide, fluticasone propionate is a glucocotricosteroid, and like formoterol, sameterol xinafoate is a beta-2

agonist, thus the comparison between the Carling et al. prior art and Exhibit 3 is proper.

The Examiner disagrees because it is noted that evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention. See, e.g., In re Kulling, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 777 (Fed. Cir. 1983). The present claims are drawn to an admixture of budesonide and formoterol, in which Exhibit 3 is a mixture of fluticasone and sameterol xinafoage. Although they are the categorized as a glucocotricosteroid and a beta-2 agonist, the drugs are not the same drugs presented by the Applicant or Carling et al. Thus, Exhibit 3 is not persuasive to overcome any of the rejections of record.

Exhibit 4 is a journal article by O'Bryne et al. ("Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma," Am J Respir Crit Car Med, 2005, vol. 171, pp. 129-136). The article teaches asthma control is improved by combining inhaled corticosteroids with long-acting beta agonists. However, fluctuating asthma control still occurs. O'Bryne et al. found that patients administered budesonide/formoterol (bud/form) twice a day with as-needed bud/form (bud/form maintenance + relief) had prolonged the time to first severe exacerbation, resulting in a 45-47% lower exacerbation risk versus bud/form + terbutaline (SABA) administered twice a day. Bud/form maintenance + relief also prolonged the time to the first, second and third exacerbation requiring medical intervention, reduced severe exacerbation rate, and improved symptoms, awakenings, and lung function compared with both fixed dosing regimens (see Abstract.) Additionally, only 16% of patients who used the product for rescue purposes (bud/form maintenance + relief) experienced severe exacerbations, compared to 27% or 28% of the patients administered bud and SABA or bud/form and SABA. The Applicant points to the above results as evidence of Applicant's stated "surprising results." In view of this article, it is irrefutable

that the presently claimed method produces results that are unexpectedly better than what the prior art methods produce.

The Examiner disagrees because it is noted that evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention. See, e.g., In re Kulling, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 777 (Fed. Cir. 1983). The present claims are drawn to an admixture of budesonide and formoterol administered twice per day as a maintenance dose, and one or more additional dose on an irregular, as-needed bases for rescue purposes. The closest prior art, Carling et al., teaches an admixture of budesonide and formoterol administered in an intended dosage of twice per day. The O'Bryne reference teaches differences between the Applicant's invention and combinations of budesonide, formoterol and terbutaline or budesonide and terbutaline, administered twice a day. The comparison is not the closest to the cited art because an additional drug (terbutaline) is administered other than budesonide and formoterol. Additionally, the court finds no support for proposition which would require inoperativeness of a device when operating over a different range from that claimed, in order to support finding of criticality for claimed range" see In re Waymouth and Koury, 182 USPQ 290 (C.C.P.A. 1974). In order for the Applicant to show an unexpected result, there must be a difference in kind, rather than in degree between the Applicant's administration and the prior art.

Exhibit 5 is an editorial by Barnes ("A Single Inhaler for Asthma?" Am J Respir Crit Car Med, 2005, vol. 171, pp. 95-96). Dr. Barnes states his

opinion of O'Bryne et al., in that "the study by O'Bryne and his colleagues may lead to changes in the paradigm of asthma management..." (see page 95, last paragraph.) Dr. Barnes also states that the remarkable, and somewhat unexpected, finding was that the treatment with combination inhaler for both maintenance and relief markedly reduced the number of severe exacerbations (the primary outcome measure) over the 1-year treatment period compared with other treatments, but also reduced the need for oralcorticosteroids, improved symptom control, and lung function compared with the other treatment regimens of a four-fold greater dose of budesonide alone or budesonide and formoterol at the same dose of the bud/form maintenance + bud/form relief. Both of the other treatment regimens are administered with terbutaline as needed (see page 95, column 1, last paragraph). The concern about the improved regimen is that some patients might end up using the combination inhaler frequently and therefor receive an unacceptably high dose of inhaled corticosteroid. However, this was not the case, as the mean number of additional doses of combination inhaler was only one does per day and very few patients used high doses (see page 95, column 1, last line to column 2, first paragraph). The Applicant argues that the statements by Dr. Barnes, including the characterization of the O'Byrne et al. report as including "surprisingly good results," were made in 2005, twelve years after the Carling et al. reference was published. In the heavily researched field of asthma treatment, if Applicant's invention had indeed been obvious from Carling et al.'s teachings, it would not, twelve years later, have been regarded as the radical departure from the norm implied by the Barnes editorial. Thus, the Applicant's treatment as "remarkable" and the results as "surprisingly good" certainly qualifies as strong evidence of nonobviousness.

The Examiner disagrees because it is noted that evidence of unexpected results is required to be reasonably commensurate in scope with the claimed invention. See, e.g., In re Kulling, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 777 (Fed. Cir. 1983). The present claims are drawn to an admixture of budesonide and formoterol administered twice per day as a maintenance dose, and one or more additional dose on an irregular, as-need bases for rescue purposes. The closest prior art, Carling et al., teaches an admixture of

budesonide and formoterol administered in an intended dosage of twice per day. The O'Bryne reference teaches differences between the Applicant's invention and combinations of budesonide, formoterol and terbutaline or budesonide and terbutaline, administered twice a day. The comparison is not the closest to the cited art because an additional drug (terbutaline) is administered other than budesonide and formoterol. Additionally, the court finds no support for proposition which would require inoperativeness of a device when operating over a different range from that claimed, in order to support finding of criticality for claimed range" see In re Waymouth and Koury, 182 USPQ 290 (C.C.P.A. 1974). In order for the Applicant to show an unexpected result, there must be a difference in kind, rather than in degree between the Applicant's administration and the prior art. Additionally, the safety of administering additional doses of the combination inhaler has been addressed above. Furthermore, the potential concern of providing additional dosages of the combination inhaler are also addressed by Dr. Barnes, which support the Examiner's arguments that as the mean number of additional doses of combination inhaler was only one does per day and very few patients used high doses (see page 95, column 2, first paragraph). Thus, if the patient is experiencing acute asthmatic attack even with ongoing twice a day dosing regimen, the patient can still safely inhale an additional 6 inhalations without going over the maximum suitable daily dosage. The skilled artisan would have been motivated to instruct the patient to use the Carling et al. composition as needed on the bases of up to 8 inhalations a day is for reasonable expectation of successfully achieving maximum benefit in the treatment of asthma. Thus, the patient could administer an as-needed

dose up to the maximum amount of doses determined by the physician. Additionally, as the Applicant provided in Exhibit 2, the dose of the budesonide and formoterol combined inhaler should be titrated to the lowest dose at which effective control of symptoms is maintained" (see page 1, section F).

Reason to carry out the claimed methods:

> The Applicant argues that the Examiner has articulated no logical reason why one of ordinary skill would alter the teachings of Carling et al. to result in the claimed methods, and one of ordinary skill in the art would not have had a reasonable expectation that the claimed methods would succeed. Besides the Examiner's position regarding motivation set forth at page 10 of the Office Action, Applicant believes these interpretations of Carling et al.'s teachings do not accurately characterized how one of ordinary skill in the art of asthma treatment would have read this reference. For example, the Examiner has made the unwarranted assumption that every asthma patient will be able to "safely inhale" even the high end of the ranges of "suitable daily doses" set forth at page 6, lines 24-27 of Carling et al. Even if Carling et al. hadn't gone on to explain that the "particular dose" depends "strongly" on patient-specific factors, one of ordinary skill in the art of asthma treatment would clearly not have read Carling et al.'s teachings about dosage ranges as meaning all patients can safely inhale all doses up to and including the maximum. Further the Examiner's assumption is inconsistent with the knowledge in the art that budesonide are potent drugs with dangerous side effects, whose use must be carefully monitored in every patient to avoid overdosing as discussed previously. Applicant also notes that Carlin et al.'s reference to "severity of the disease" as being one of the bases for setting the amount of the twice-daily dose of the composition does not mean that the patient should be administered more doses if his/her disease is particularly severe on a given day. It simply means that the overall level of the patient's disease is one of the factors the prescribing physician should take into account in setting the twice-daily dose, such as prescribing a larger maintenance dose.

The Examiner disagrees because of the logic of obviousness has been set forth on page 10 of the previous office action and above in the response to each exhibit and in the final office action issued above. In regards to Carling et al. teaching that the particular dose depends strongly on patient-specific factors reading on that all patients can safely inhale all doses up to and including the maximum, is clearly not what one skilled in the art would interpret. Particularly because of a physician is considering several factors, each patient would be instructed on the maximum puffs that could be taken without going over the maximum daily amount of each drug. As with any non-over-the counter drug, a patient can potentially overdose, thus patient-specific factors are taken into consideration. Upon reading the Applicant's claims, the Examiner does not read that all patients can take *an infinite amount of doses for rescue purposes*. The benefit of providing the combined treatment of budesonide and formoterol is as Carling et al. teaches, to provide greater efficiency and duration of bronchodilator action, and rapid onset action, which provides rescue medicine, adequate dosing for treating asthma (see page 4, lines 4-21). Also as provided by the Applicant in Exhibit 5, Dr. Barnes comments on that the mean number of additional doses of combination inhaler was only one does per day and very few patients used high doses (see page 95, column 2, first paragraph). Thus, if the patient is experiencing acute asthmatic attack even with ongoing twice a day dosing regimen as taught by Carling et al., the patient can still safely inhale an additional 6 inhalations without going over the maximum suitable daily dosage. The above arguments also apply to the Applicant's comments on

increasing the administration versus the dosage in regards to the severity of the disease.

Expectation of Success:

> The Applicant argues that the Examiner is saying that one of ordinary skill would have a reasonable expectation of successfully treating any and all asthma patients by simply handing them an inhaler containing Carling et al.'s formoterol/budesonide composition and telling them to inhale any amount per day that they wish, up to the including the maximum daily dose of 100 μg formoterol and 4800 μg budesonide, because that will give them "maximum benefit," whatever the level of severity of their condition. Further, at least with respect to the budesonide part of this composition, Applicant has provided ample evidence that one of ordinary skill in 1997 would not have had such a reasonable expectation of success under the scenario the Examiner believes is obvious. Applicant's evidence of surprising results, long-felt unsatisfied need, and skepticism of experts is objective evidence of non-obviousness.

The Examiner disagrees because of the reason previously discussed above. The teachings of Carling et al. are taken as a whole. Applicant's evidence of surprising results, long-felt unsatisfied need, and skepticism of experts has been addressed above in the remarks for the Applicant's Exhibit 5.

> The Applicant argues that claims 16 and 19, which depend from claim 13, are patentable for at least the reasons discussed above with respect to claim 13 and the rest of the independent claims. The teachings of Aberg et al. and Ryrfeldt et al. do not make up for Carling et al.'s deficiencies as outlined above, and indeed are cited solely for their teachings concerning specific stereoisomers of the active ingredients.

The Examiner disagrees for the reasons previous discussed above. Aberg et al. and Ryrfeldt et al. are used for their teachings concerning specific stereoisomers of the Applicant's active ingredients.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kendra D. Carter whose telephone number is (571) 272-9034. The examiner can normally be reached on 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

KDC

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER